# PCOS

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## ABSTRACT

INTRODUCTION: Polycystic ovary syndrome (PCOS) is characterised by an accumulation of incompletely developed follicles in the ovaries due to anovulation. It is diagnosed in up to 10% of women attending gynaecology clinics, but the prevalence in the population as a whole is unclear. PCOS has been associated with hirsutism, infertility, acne, weight gain, type 2 diabetes, cardiovascular disease (CVD), and endometrial hyperplasia. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments in women with PCOS? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 24 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: cyproterone acetate–ethinylestradiol (co-cyprindiol), finasteride, flutamide, interventions to achieve weight loss, ketoconazole, mechanical hair removal, metformin, and spironolactone.


## QUESTIONS

What are the effects of treatments in women with PCOS? . . . . . 3

## INTERVENTIONS

### TREATMENTS

#### Likely to be beneficial

Finasteride (may be similarly effective in reducing hirsutism compared with spironolactone and cyproterone acetate–ethinylestradiol) . . . . . 8

Flutamide (may be similarly effective in reducing hirsutism compared with finasteride and spironolactone) . . . . . 12

Metformin (improved menstrual pattern compared with placebo; reduced hirsutism compared with cyproterone acetate–ethinylestradiol) . . . . . 29

Spironolactone (may be similarly effective for reducing hirsutism compared with flutamide and finasteride) . . 3 9

#### Trade off between benefits and harms

Cyproterone acetate–ethinylestradiol (co-cyprindiol; reduced hirsutism but increased risk of venous thromboembolism) . . . . . 3

#### Unknown effectiveness

Ketoconazole . . . . . 27

Mechanical hair removal . . . . . 28

Weight loss (interventions to achieve weight loss) . . 2 6

#### Covered elsewhere in Clinical Evidence

For interventions in women with infertility attributed to PCOS, see review on female infertility.

#### To be covered in future updates

Treatments for insulin resistance in women with polycystic ovary syndrome

## Key points

- PCOS is characterised by an accumulation of incompletely developed follicles in the ovaries due to anovulation, and is associated with increased ovarian androgen production. Clinical manifestations of PCOS include infrequent or absent menses, obesity, and signs of androgen excess including acne or seborrhoea.

  PCOS is diagnosed in up to 10% of women attending gynaecology clinics, but the prevalence in the population as a whole is unclear.

  PCOS has been associated with hirsutism, infertility, acne, insulin resistance, elevated serum luteinising hormone (LH) levels, weight gain, type 2 diabetes, CVD, and endometrial hyperplasia.

- Metformin in selected patients (who have abnormal LH/follicle-stimulating hormone [FSH] ratios) may improve menstrual pattern and oligomenorrhoea. The results of studies comparing metformin with placebo are conflicting for menstrual frequency and hirsutism. Metformin, alone or combined with cyproterone acetate–ethinylestradiol (co-cyprindiol), may be more effective than cyproterone acetate–ethinylestradiol alone at reducing hirsutism. Metformin combined with flutamide reduces hirsutism scores and improves menstrual frequency compared with placebo, but we don't know how the individual drugs compare with each other.

  Cyproterone acetate–ethinylestradiol may reduce hirsutism, but increases the risk of venous thromboembolism compared with placebo.

Finasteride may reduce hirsutism compared with placebo, and seems as effective as spironolactone or cyproterone acetate–ethinylestradiol. Finasteride plus cyproterone acetate–ethinylestradiol may be more effective than cyproterone acetate–ethinylestradiol alone at reducing hirsutism.

Flutamide, alone and in combination with metformin, may reduce hirsutism compared with placebo, but has been associated with adverse hepatic effects. Flutamide may reduce hirsutism compared with finasteride, but studies have given conflicting results. Flutamide and spironolactone seem equally effective at reducing hirsutism.

Combined treatment with flutamide plus cyproterone acetate–ethinylestradiol may reduce the proportion of women with oligomenorrhoea compared with flutamide alone.

- We don't know whether weight loss improves clinical outcomes in women with PCOS.

We don't know whether ketoconazole or hair removal treatments are effective at reducing hirsutism compared with other treatments. Mechanical hair removal with certain types of lasers may be effective in the short term (6 months), but longer-term effects are less clear.

**DEFINITION**

Polycystic ovary syndrome (PCOS; Stein–Leventhal syndrome; sclerocystic ovarian disease) is by definition a syndrome for which there is no single diagnostic criterion to confirm clinical diagnosis. It is diagnosed as the presence of ultrasound evidence of polycystic ovaries or hyperandrogenism. PCOS is characterised by an accumulation of incompletely developed follicles in the ovaries due to anovulation, and is associated with increased ovarian androgen production. Clinical manifestations include infrequent or absent menses, obesity, and signs of androgen excess which include acne or seborrhoea. Women with PCOS commonly have insulin resistance and elevated serum luteinising hormone (LH) levels, and are at an increased risk of type II diabetes and cardiovascular events.

**INCIDENCE/ PREVALENCE**

PCOS is diagnosed in 4%–10% of women attending gynaecology clinics in resource-rich countries, [1] [2] but this figure may not reflect the true prevalence, as there have been no specific population-based studies, and the criteria used for diagnosis are varied. An international consensus definition of PCOS defined a set of agreed criteria used for diagnosis. [3] Studies since then suggest a greater than 20% incidence and prevalence of PCOS in overweight and obese women. [4]

**AETIOLOGY/ RISK FACTORS**

The aetiology is unknown. Genetic factors may play a part, but the exact mechanisms are unclear. Two studies found some evidence of familial aggregation of hyperandrogenaemia (with or without oligomenorrhoea) in first-degree relatives of women with PCOS. [2] [5] In the first study, 22% of sisters of women with PCOS fulfilled diagnostic criteria for PCOS. [2] In the second study, of the 78 mothers and 50 sisters evaluated clinically, 19 (24%) mothers and 16 (32%) sisters had PCOS. [5]

The diagnosis excludes secondary causes, such as androgen-producing neoplasm, hyperprolactinaemia, and adult-onset congenital adrenal hyperplasia. [1] It is characterised by irregular menstrual cycles, scanty or absent menses, multiple small cysts on the ovaries (polycystic ovaries), mild hirsutism, and infertility. Many women also have insulin resistance, acne, and weight gain. [1] Until recently, there was no overall consensus on the criteria for diagnosing PCOS. In some studies, it has been diagnosed based on the ultrasound findings of polycystic ovaries rather than on clinical criteria. An international consensus definition of PCOS has now been published, which defines PCOS as at least two of the following criteria: reduced or no ovulation; clinical and/or biochemical signs of excessive secretion of androgens; and/or polycystic ovaries (the presence of at least 12 follicles measuring 2–9 mm in diameter, an ovarian volume in excess of 10 mL, or both). [3]

**PROGNOSIS**

There is some evidence that women with PCOS are at increased risk of developing type 2 diabetes and cardiovascular disorders secondary to hyperlipidaemia, compared with women who do not have PCOS. [6] However, although there is a higher risk of cardiovascular disorders, there is no apparent increase in risk of mortality. [7] There is some evidence that oligomenorrhoeic and amenorrhoeic women are at increased risk of developing endometrial hyperplasia and, later, endometrial carcinoma. [8] [9]

**AIMS OF INTERVENTION**

To reduce hirsutism and restore regular menstrual cycle, with minimal adverse effects.

**OUTCOMES**

**Hirsutism**: in women with hirsutism, measured by objective scales of reduction in hirsutism such as the Ferriman–Gallwey scale, which quantifies the extent of hair growth in nine anatomical sites, scoring 0 (no hair) to 4 (maximal growth), with a maximum score of 36; personal perception of reduction in hirsutism; adverse effects of treatment. **Menstruation frequency** in women with oligomenorrhoea. **Adverse effects** of treatment.

**METHODS**

*Clinical Evidence* search and appraisal December 2007. The following databases were used to identify studies for this review: Medline 1966 to December 2007, Embase 1980 to December 2007,

and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 4. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single-blinded, and containing more than 20 individuals of whom more than 90% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. For studies on hirsutism and weight loss we included open/unblinded studies. Hirsute outcomes required at least 3 months' follow-up to be eligible for inclusion. We also searched *WHO Pharmaceuticals Newsletter* 1997–2007 for safety alerts regarding the included drugs. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the review as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 43 ). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

## QUESTION What are the effects of treatments in women with PCOS?

## OPTION CYPROTERONE ACETATE–ETHINYLESTRADIOL (CO-CYPRINDIOL)

- For GRADE evaluation of interventions for PCOS, see table, p 43 .
- Cyproterone acetate–ethinylestradiol (co-cyprindiol) may be more effective when combined with metformin at reducing hirsutism than cyproterone acetate–ethinylestradiol alone.
- Cyproterone acetate–ethinylestradiol is associated with an increased risk of venous thromboembolism.

### Benefits and harms

**Cyproterone acetate–ethinylestradiol versus placebo:**

We found one systematic review (search date 2002, 1 RCT) comparing cyproterone acetate–ethinylestradiol versus placebo. [10]

#### Hirsutism

*Cyproterone acetate–ethinylestradiol compared with placebo* Cyproterone acetate–ethinylestradiol may be more effective than placebo at reducing hair growth at 12 months in women with PCOS (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [10] Systematic review | 20 women with PCOS and hirsutism, aged 17–31 years<br>Data from 1 RCT | **Subjective hair growth , 12 months**<br>with cyproterone acetate–ethinylestradiol<br>with placebo<br>Absolute results not reported | OR 45<br>95% CI 2 to 1006 | ●●● | cyproterone acetate–ethinylestradiol |

#### Menstrual frequency

No data from the following reference on this outcome. [10]

### Adverse effects

No data from the following reference on this outcome. [10]

### Cyproterone acetate–ethinylestradiol versus ketoconazole, spironolactone, or cyproterone acetate–ethinylestradiol plus sequential cyproterone acetate:

We found one systematic review (search date 2002). [10] The RCT identified by the review is an open-label RCT and does not meet *Clinical Evidence* inclusion criteria, and is not discussed further.

### Cyproterone acetate–ethinylestradiol versus combined oral contraceptives:

We found no systematic review but found one RCT. [11]

### Hirsutism

*Cyproterone acetate–ethinylestradiol compared with combined oral contraceptives* We don't know whether cyproterone acetate–ethinylestradiol is more effective than desogestrel–ethinylestradiol at reducing hirsutism at 6 months in adolescents with PCOS (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [11]<br>RCT | 28 adolescent girls (aged 14–19 years) with PCOS | **Ferriman–Gallwey score from baseline , 12 months**<br>with cyproterone acetate–ethinylestradiol<br>with combined oral contraceptive<br>Absolute results reported graphically<br>Regimens involved ethinylestradiol 35 micrograms daily plus cyproterone acetate 2 mg daily *v* ethinylestradiol 30 micrograms daily plus desogestrel 0.15 mg daily for 21 days followed by a 7-day rest, for a period of 12 months | No direct comparison between groups<br>P <0.05 for change from baseline in hirsutism with either treatment | | |

### Menstrual frequency

No data from the following reference on this outcome. [11]

### Adverse effects

No data from the following reference on this outcome. [11]

### Cyproterone acetate–ethinylestradiol versus metformin:

We found one systematic review (search date 2005, 6 RCTs), [12] which identified two RCTs (52 women) comparing cyproterone acetate–ethinylestradiol versus metformin in women with PCOS.

## Hirsutism

*Cyproterone acetate–ethinylestradiol compared with metformin* We don't know whether cyproterone acetate–ethinylestradiol is more effective than metformin at reducing hirsutism at 12 months in women with PCOS (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [12]<br>Systematic review | 52 women with PCOS, 35 analysed<br>2 RCTs in this analysis<br>18 of the 52 women randomised were clinically diagnosed with hirsutism (defined as Ferriman–Gallwey score >7)<br>The review included open label trials | **Ferriman–Gallwey hirsutism scores**<br>with cyproterone acetate–ethinylestradiol<br>with metformin<br>Absolute results not reported | WMD 2.66<br>95% CI –0.33 to +5.66 | ⟷ | Not significant |

## Menstrual frequency

No data from the following reference on this outcome. [12]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [12]<br>Systematic review | 104 women<br>3 RCTs in this analysis | **Severe adverse effects**<br>10/52 (19%) with cyproterone acetate–ethinylestradiol<br>0/52 (0%) with metformin<br>Severe adverse effects included weight gain, high blood pressure, depression, chest pain, and headache | RR 0.13<br>95% CI 0.02 to 0.69 | ●●● | metformin |
| [12]<br>Systematic review | 104 women<br>3 RCTs in this analysis<br>The RCT reported that 18 of the 52 women randomised were clinically diagnosed with hirsutism (defined as Ferri- | **Gastrointestinal adverse effects**<br>0/52 (0%) with cyproterone acetate–ethinylestradiol<br>5/52 (10%) with metformin | RR 4.33<br>95% CI 0.76 to 24.58 | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | man–Gallwey score >7) | | | | |

**Cyproterone acetate–ethinylestradiol plus finasteride versus cyproterone acetate–ethinylestradiol alone:**
We found no systematic review but we found one RCT. [13]

### Hirsutism

*Cyproterone acetate–ethinylestradiol plus finasteride compared with cyproterone acetate–ethinylestradiol alone*
Cyproterone acetate–ethinylestradiol plus finasteride may be more effective than cyproterone acetate–ethinylesradiol alone at reducing hirsutism at 3 to 6 months in women with PCOS (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [13]<br>RCT | 50 women, 20 with PCOS | **Reduction in hirsutism , 3 to 6 months**<br>with cyproterone acetate–ethinylestradiol plus finasteride<br>with cyproterone acetate–ethinylestradiol alone<br>Absolute results reported graphically | P <0.05 at both time points | ○○○ | cyproterone acetate–ethinylestradiol plus finasteride |

### Menstrual frequency

No data from the following reference on this outcome. [13]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Reduced libido** | | | | | |
| [13]<br>RCT<br>**Crossover design** | 50 women, 20 with PCOS | **Reduced libido , 6 months**<br>20% with cyproterone acetate–ethinylestradiol plus finasteride<br>10% with cyproterone acetate–ethinylestradiol alone<br>Absolute numbers not reported | P <0.05 | ○○○ | cyproterone acetate–ethinylestradiol alone |

**Cyproterone acetate–ethinylestradiol versus finasteride:**
See option on finasteride, p 8 .

### Cyproterone acetate–ethinylestradiol plus flutamide versus cyproterone acetate–ethinylestradiol alone:

See option on flutamide, p 12 .

### Cyproterone acetate–ethinylestradiol plus metformin versus cyproterone acetate–ethinylestradiol alone:

We found one systematic review (search date 2005, 6 RCTs), [13] which identified one RCT comparing cyproterone acetate–ethinylestradiol plus metformin versus cyproterone acetate–ethinylestradiol alone.

#### Hirsutism

*Cyproterone acetate–ethinylestradiol plus metformin compared with cyproterone acetate–ethinylestradiol alone*

Cyproterone acetate–ethinylestradiol plus metformin may be more effective than cyproterone acetate–ethinylestradiol alone at reducing hirsutism scores at 4 months (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [13]<br>Systematic review | 40 non-obese women, with and without clinically diagnosed hirsutism<br>Data from 1 RCT<br>The RCT did not report the number of women who were clinically diagnosed with hirsutism (Ferriman–Gallwey score >7) | **Reduction in Ferriman–Gallwey score , 4 months**<br>with cyproterone acetate–ethinylestradiol (ethinylestradiol 35 micrograms daily plus cyproterone acetate 2 mg daily) plus metformin<br>with cyproterone acetate–ethinylestradiol<br>Absolute results not reported | WMD –2.82<br>95% CI –5.47 to –0.17 | ○○○ | cyproterone acetate–ethinylestradiol plus metformin |

#### Menstrual frequency

No data from the following reference on this outcome. [13]

#### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [13]<br>Systematic review | 40 non-obese women, with and without clinically diagnosed hirsutism<br>Data from 1 RCT | **Minor gastrointestinal effects**<br>4/20 (20%) with cyproterone acetate–ethinylestradiol plus metformin<br>0/20 (0%) with cyproterone acetate–ethinylestradiol | RR 9.00<br>95% CI 0.52 to 156.91 | ⟷ | Not significant |

**Further information on studies**

[14] Cyproterone acetate–ethinylestradiol is associated with an increased risk of venous thromboembolism.

**Comment:** None of the RCTs assessed participant satisfaction or compliance.

## OPTION FINASTERIDE

- For GRADE evaluation of interventions for PCOS, see table, p 43 .
- Finasteride may reduce hirsutism compared with placebo, and seems as effective as spironolactone or cyproterone acetate–ethinylestradiol.
- Finasteride plus cyproterone acetate–ethinylestradiol may be more effective than cyproterone acetate–ethinylestradiol alone at reducing hirsutism.

## Benefits and harms

### Finasteride versus placebo:

We found two RCTs. [15] [16]

#### Hirsutism

*Finasteride compared with placebo* Finasteride may be more effective than placebo at reducing hirsutism at 6 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [15]<br>RCT | 24 women, 14 with PCOS | **Mean Ferriman–Gallwey score , 6 months**<br>6.7 with finasteride (5 mg daily)<br>10.6 with placebo | P <0.01 | ○○○ | finasteride |
| [16]<br>RCT<br>**4-armed trial** | 40 women, 21 with PCOS<br>The remaining arms evaluated spironolactone (100 mg daily) and flutamide (250 mg daily) | **Mean reduction in Ferriman–Gallwey score , 6 months**<br>with finasteride (5 mg daily)<br>with placebo<br>Absolute results reported graphically<br>20 women in this analysis | P <0.01 for finasteride *v* placebo | ○○○ | finasteride |

#### Menstrual frequency

No data from the following reference on this outcome. [15] [16]

#### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [15]<br>RCT | 24 women, 14 with PCOS | **Dizziness**<br>3/12 (25%) with finasteride<br>1/12 (8%) with placebo | Significance not assessed | | |

No data from the following reference on this outcome. [16]

### Finasteride versus flutamide:

We found four RCTs. [16] [17] [18] [19]

#### Hirsutism

*Finasteride compared with flutamide* We don't know how finasteride and flutamide compare at reducing hirsutism at 9 months in women with PCOS (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [16] RCT **4-armed trial** | 40 women, 21 with PCOS<br>The remaining arms evaluated spironolactone 100 mg daily and placebo | **Hirsutism , 6 months**<br>with finasteride 5 mg daily<br>with flutamide 250 mg daily<br>Absolute results reported graphically<br>20 women in this analysis | Reported as not significant for finasteride *v* flutamide<br>P value not reported | ⟷ | Not significant |
| [17] RCT | 44 women with PCOS | **Mean reduction in Ferriman–Gallwey score , 6 months**<br>25% with finasteride (5 mg daily)<br>20% with flutamide (250 mg twice daily)<br>Absolute numbers not reported | Reported as not significant<br>P value between groups not reported<br>P <0.05 *v* baseline in both groups | ⟷ | Not significant |
| [18] RCT | 110 women aged 18–29 years, 64 with PCOS | **Mean reduction in Ferriman–Gallwey score from baseline , 12 months**<br>5.0 with finasteride<br>9.3 with flutamide | P <0.01 | ○○○ | flutamide |
| [19] RCT | 70 women, 36 with PCOS, 34 with idiopathic hirsutism | **Percentage reduction in Ferriman–Gallwey score , 12 months**<br>41% with finasteride (5 mg daily)<br>71% with flutamide (250 mg daily)<br>Absolute numbers not reported | No direct comparison between groups<br>P <0.01 *v* baseline in both groups | | |

#### Menstrual frequency

No data from the following reference on this outcome. [16] [17] [18] [19]

#### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [18] RCT | 110 women aged 18–29 years, 64 with PCOS | **Gastric discomfort**<br>4 with finasteride<br>0 with flutamide | P value not reported | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | Absolute results not reported | | | |
| [19] RCT | 70 women, 36 with PCOS, 34 with idiopathic hirsutism | **Dry skin** 13/55 (24%) with finasteride 37/55 (67%) with flutamide | P value not reported | | |
| [19] RCT | 70 women, 36 with PCOS, 34 with idiopathic hirsutism | **Decreased libido** 6/55 (11%) with finasteride 9/55 (16%) with flutamide | P value not reported | | |
| [19] RCT | 70 women, 36 with PCOS, 34 with idiopathic hirsutism | **Gastrointestinal disorders** 7/55 (13%) with flutamide Data for finasteride not reported | P value not reported | | |

No data from the following reference on this outcome. [16] [17]

### Finasteride versus spironolactone:

See option on spironolactone, p 39 .

### Finasteride versus cyproterone acetate–ethinylestradiol:

We found one RCT comparing finasteride versus cyproterone acetate–ethinylestradiol for 9 months. [20]

#### Hirsutism

*Finasteride compared with cyproterone acetate–ethinylestradiol* We don't know how finasteride and cyproterone acetate–ethinylestradiol compare at improving hirsutism in women with PCOS (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [20] RCT | 40 women, 29 with PCOS and 11 with idiopathic hirsutism | **Mean modified Ferriman–Gallwey score , 9 months** 11.3 with finasteride (5 mg/day) 11.4 with cyproterone acetate–ethinylestradiol (cyproterone acetate 25 mg/day on days 5–14 plus ethinylestradiol 20 micrograms/day on days 5–25) Hirsutism decreased significantly from baseline to 9 months in both groups; mean reduction in modified Ferriman–Gallwey score from baseline 12.4 with finasteride (P <0.001) *v* 10.9 with cyproterone acetate–ethinylestradiol. P <0.001 for either group *v* baseline | P = 0.2 for finasteride *v* cyproterone acetate–ethinylestradiol | ⟷ | Not significant |
| [20] RCT | 40 women, 29 with PCOS and 11 with idiopathic hirsutism | **Improvement in mean modified Ferriman–Gallwey score from baseline , 9 months** 48% with finasteride (5 mg/day) | P = 0.2 | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | 51% with cyproterone acetate–ethinylestradiol (cyproterone acetate 25 mg/day on days 5–14 plus ethinylestradiol 20 micrograms/day on days 5–25)<br>Absolute numbers not reported | | | |

**Menstrual frequency**

No data from the following reference on this outcome. [20]

**Adverse effects**

No data from the following reference on this outcome. [20]

**Finasteride plus cyproterone acetate–ethinylestradiol versus cyproterone acetate–ethinylestradiol alone:**
See option on cyproterone acetate-ethinylestradiol, p 3 .

**Finasteride plus spironolactone versus spironolactone alone:**
We found no systematic review but found one small RCT. [21]

**Hirsutism**

*Finasteride plus spironolactone compared with spironolactone alone* Finasteride plus spironolactone may be more effective than spironolactone alone at reducing hirsutism at 1 year (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [21]<br>RCT | 65 women with hirsutism; 34 women with PCOS | **Percentage of reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>51.3% with spironolactone (100 mg daily) plus finasteride (5 mg daily)<br>36.6% with spironolactone alone (100 mg daily)<br>Absolute numbers not reported | No direct comparison between groups<br>P <0.005 for change from baseline in both groups | | |

**Menstrual frequency**

No data from the following reference on this outcome. [21]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Polymenorrhoea** | | | | | |
| [21]<br>RCT | 65 women with hirsutism; 34 women with PCOS | **Polymenorrhoea**<br>47% with finasteride plus spironolactone<br>61% with spironolactone<br>Absolute numbers not reported | P value not reported | | |

**Further information on studies**

[18] The RCT suggested that flutamide may be associated with hepatotoxicity, but the risk was lower with flutamide 250 mg daily, as given in the trial, than with finasteride.

**Comment:** Although the RCTs included women with idiopathic hirsutism (women with hirsutism who have regular menstrual cycles and normal circulating androgen levels), it is likely that the results are generalisable to women with hirsutism associated with PCOS.

## OPTION FLUTAMIDE

- For GRADE evaluation of interventions for PCOS, see table, p 43 .
- Flutamide, alone and in combination with metformin, may reduce hirsutism compared with placebo, but has been associated with adverse hepatic effects. Flutamide may reduce hirsutism compared with finasteride, but studies have given conflicting results. Flutamide and spironolactone seem equally effective at reducing hirsutism.
- Combined treatment with flutamide plus cyproterone acetate–ethinylestradiol may reduce the proportion of women with oligomenorrhoea compared with flutamide alone.

## Benefits and harms

**Flutamide versus placebo:**

We found four RCTs. [16] [22] [23] [24]

### Hirsutism

*Flutamide compared with placebo* Flutamide may be more effective at improving hirsutism at 6 to 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [16]<br>RCT<br>**4-armed trial** | 40 women, 21 with PCOS<br>The remaining arms evaluated finasteride (5 mg daily) and spironolactone (100 mg daily) | **Mean reduction in Ferriman–Gallwey score , 6 months**<br>with flutamide (250 mg daily)<br>with placebo<br>Absolute results reported graphically<br>20 women in this analysis | P <0.01 for flutamide *v* placebo | ○○○ | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Mean reduction in Ferriman–Gallwey score , 6 months**<br>with flutamide<br>with placebo<br>Absolute results reported graphically<br>Number of women in this analysis was not reported | P = 0.051 for comparison between groups<br>Flutamide significantly reduced scores from baseline (no further data reported) | ⟷ | Not significant |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Mean reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>14.6 to 8.4 with flutamide<br>9.3 to 8.0 with placebo<br>36 women in this analysis | P <0.001 | ○○○ | flutamide |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 | **Mean reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>14.6 to 5.7 with flutamide<br>9.3 to 8.0 with placebo<br>36 women in this analysis | P <0.001 | ○○○ | flutamide |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | | | | |
| [24]<br>RCT<br>**4-armed trial** | 131 women with PCOS or idiopathic hirsutism and with moderate to severe hirsutism, number of women with PCOS not reported<br>The remaining arms evaluated flutamide (250 mg) and flutamide (375 mg)<br>Women in all four groups also received an oral contraceptive pill | **Mean reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>19.28 to 9.12 with flutamide (125 mg)<br>18.35 to 13.06 with placebo<br>119 women in this analysis | Reported as significant<br>P value not reported<br>The RCT carried out an ITT analysis (ITT population not defined). However, only 65% of women completed the study | ○○○ | flutamide |
| [24]<br>RCT<br>**4-armed trial** | 131 women with PCOS or idiopathic hirsutism and with moderate to severe hirsutism, number of women with PCOS not reported<br>The remaining arms evaluated flutamide (125 mg) and flutamide (375 mg)<br>Women in all four groups also received an oral contraceptive pill | **Mean reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>18.72 to 9.52 with flutamide (250 mg)<br>18.35 to 13.06 with placebo<br>119 women in this analysis | Reported as significant<br>P value not reported<br>The RCT carried out an ITT analysis (ITT population not defined). However, only 65% of women completed the study | ○○○ | flutamide |
| [24]<br>RCT<br>**4-armed trial** | 131 women with PCOS or idiopathic hirsutism and with moderate to severe hirsutism, number of women with PCOS not reported<br>The remaining arms evaluated flutamide (125 mg) and flutamide (250 mg)<br>Women in all four groups also received an oral contraceptive pill | **Mean reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>18.00 to 9.29 with flutamide (375 mg)<br>18.35 to 13.06 with placebo<br>119 women in this analysis | Reported as significant<br>P value not reported<br>The RCT carried out an ITT analysis (ITT population not defined). However, only 65% of women completed the study | ○○○ | flutamide |

### Menstrual frequency

*Flutamide compared with placebo* We don't know whether flutamide is more effective than placebo at improving menstrual frequency (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Menstrual frequency** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Change in menstrual frequency from baseline , 6 months**<br>with flutamide (250 mg twice daily)<br>with placebo<br>Absolute results reported graphically<br>Number of women in this analysis not reported | No direct comparison between groups<br>P = 0.036 for change from baseline with flutamide<br>Reported as not significant for change from baseline with placebo | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in mean menstrual frequency from baseline , 6 months**<br>3.7 to 4.8 with flutamide<br>2.7 to 3.2 with placebo<br>36 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide<br>P <0.05 for change from baseline with placebo | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; | **Change in menstrual frequency from baseline , 12 months**<br>3.7 to 5.0 with flutamide<br>2.7 to 3.2 with placebo<br>36 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide<br>P <0.05 for change from baseline with placebo | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | flutamide: 250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | | | | |

No data from the following reference on this outcome. [24] [16]

**Adverse effects**

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [24]<br>RCT | 131 women with PCOS or idiopathic hirsutism and with moderate to severe hirsutism, number of women with PCOS not reported | **Adverse effects**<br>with flutamide<br>with placebo<br>Absolute results not reported<br>Most frequent adverse effects reported: upper respiratory tract infection (9%), dry skin (9%), headache (7%), nausea and vomiting (6%), and diarrhoea (4%). Five women withdrew from the study because of clinically important laboratory abnormalities (hyperglycaemia, leukopenia, and elevated transaminases) | Similar rates of adverse effects with flutamide and placebo<br>P value not reported | | |

No data from the following reference on this outcome. [16] [22] [23]

### Flutamide versus finasteride:

See option on finasteride, p 8 .

### Flutamide versus metformin:

We found two RCTs comparing four interventions: flutamide (250 mg twice daily), metformin (850 mg twice daily), metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily), and placebo. [22] [23]

## Hirsutism

*Flutamide compared with metformin* We don't know how flutamide and metformin compare at reducing hirsutism scores at 6 and at 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily) and placebo<br>All women were given a low-calorie (1200–1400kcal/day) diet starting 1 month before treatment | **Reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>with flutamide (250 mg twice daily)<br>with metformin (850 mg twice daily)<br>Absolute results reported graphically | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide<br>P = 0.022 for change from baseline with metformin | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily) and placebo<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Mean reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>14.6 to 8.4 with flutamide (250 mg twice daily)<br>13.0 to 10.9 with metformin (850 mg twice daily)<br>37 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide<br>P <0.01 for change from baseline with metformin | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily) and placebo | **Mean reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>14.6 to 5.7 with flutamide (250 mg twice daily)<br>13.0 to 10.4 with metformin (850 mg twice daily)<br>37 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide<br>P <0.01 for change from baseline with metformin | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br><br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | | | | |

### Menstrual frequency

*Flutamide compared with metformin* We don't know whether flutamide is more effective than metformin at improving menstrual frequency at 6 to 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Menstrual frequency** | | | | | |
| [22]<br><br>RCT<br><br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br><br>The remaining arms evaluated metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily) and placebo<br><br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in menstrual frequency from baseline , 6 months**<br><br>with flutamide (250 mg twice daily)<br><br>with metformin (850 mg twice daily)<br><br>Absolute results reported graphically<br><br>Number of women in this analysis not reported | No direct comparison between groups<br><br>P = 0.036 for change from baseline with flutamide<br><br>P value reported as significant for change from baseline with metformin | | |
| [23]<br><br>RCT<br><br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br><br>The remaining arms evaluated metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily) and placebo<br><br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in | **Mean increase in the number of menses from baseline , 6 months**<br><br>3.7 to 4.8 with flutamide (250 mg twice daily)<br><br>2.6 to 4.3 with metformin (850 mg twice daily)<br><br>37 women in this analysis | No direct comparison between groups<br><br>P <0.001 for change from baseline with flutamide<br><br>P <0.01 for change from baseline with metformin | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | | | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily) and placebo<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Mean increase in the number of menses from baseline , 12 months**<br>3.7 to 5.0 with flutamide (250 mg twice daily)<br>2.6 to 4.6 with metformin (850 mg twice daily)<br>37 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide<br>P <0.001 for change from baseline with metformin | | |

### Adverse effects

No data from the following reference on this outcome. [23] [22]

### Flutamide versus spironolactone:

We found one RCT, which compared four interventions: flutamide 250 mg daily, finasteride 5 mg daily, spironolactone 100 mg daily, and placebo for 6 months. [16]

### Hirsutism

*Flutamide compared with spironolactone* We don't know how flutamide and spironolactone compare at reducing hirsutism at 6 months in women with PCOS (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [16]<br>RCT<br>**4-armed trial** | 40 women, 21 with PCOS | **Hirsutism , 6 months**<br>with flutamide 250 mg daily<br>with finasteride 5 mg daily<br>with spironolactone 100 mg daily<br>with placebo<br>Absolute results reported graphically<br>Number of women in this analysis not reported | Reported as not significant for difference among groups<br>P value not reported<br>The RCT may have been underpowered to detect a clinically important difference among treatments<br>All active treatments reduced hirsutism from baseline | ⟷ | Not significant |

### Menstrual frequency

No data from the following reference on this outcome. [16]

### Adverse effects

No data from the following reference on this outcome. [16]

### Flutamide versus flutamide plus cyproterone acetate–ethinylestradiol:

We found no systematic review or RCTs.

### Flutamide versus flutamide plus metformin:

We found two RCTs comparing four interventions: flutamide (250 mg twice daily), metformin (850 mg twice daily), metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily), and placebo. [22] [23]

### Hirsutism

*Flutamide compared with flutamide plus metformin* We don't know how flutamide and flutamide plus metformin compare at reducing hirsutism scores at 6 and 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hisutism** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and placebo<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>with flutamide (250 mg twice daily)<br>with flutamide plus metformin (flutamide 250 mg twice daily plus metformin 850 mg twice daily)<br>Absolute results reported graphically<br>Number of women in this analysis not reported | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide alone<br>P <0.001 for change from baseline with flutamide plus metformin | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and placebo<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>14.5 to 7.9 with flutamide plus metformin<br>14.6 to 8.4 with flutamide alone<br>37 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide plus metformin<br>P <0.001 for change from baseline with flutamide alone | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and placebo<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>14.5 to 7.9 with flutamide plus metformin<br>14.6 to 5.7 with flutamide alone<br>37 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide plus metformin<br>P <0.001 for change from baseline with flutamide alone | | |

### Menstrual frequency

*Flutamide compared with flutamide plus metformin* We don't know how flutamide and flutamide plus metformin compare at improving menstrual frequency at 6 and 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Menstrual frequency** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and placebo<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in menstrual frequency from baseline , 6 months**<br>with flutamide plus metformin<br>with flutamide alone<br>Absolute results reported graphically<br>Number of women in this analysis not reported | No direct comparison between groups<br>P = 0.04 for change from baseline with flutamide plus metformin<br>P <0.001 for change from baseline with flutamide alone | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and placebo<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in menstrual frequency from baseline , 6 months**<br>2.8 to 4.3 with flutamide plus metformin<br>2.7 to 3.2 with flutamide alone<br>Absolute results reported graphically<br>37 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide plus metformin<br>P <0.01 for change from baseline with flutamide alone | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and placebo<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited | **Increase in menstrual frequency from baseline , 12 months**<br>2.8 to 5.8 with flutamide plus metformin<br>2.7 to 3.2 with flutamide alone<br>37 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with flutamide plus metformin<br>P <0.001 for change from baseline with flutamide alone | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | | | | |

### Adverse effects

No data from the following reference on this outcome. [22] [23]

### Flutamide plus metformin versus placebo:

We found two RCTs comparing four interventions: flutamide (250 mg twice daily), metformin (850 mg twice daily), metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily), and placebo. [22] [23]

### Hirsutism

*Flutamide plus metformin compared with placebo* Flutamide plus metformin may be more effective than placebo at reducing hirsutism scores at 6 and 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and flutamide (250 mg twice daily)<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Reduction in Ferriman–Gallwey scores from baseline**<br>with flutamide plus metformin (flutamide 250 mg twice daily; metformin 850 mg twice daily)<br>with placebo<br>Absolute results reported graphically<br>Number of women in this analysis not reported | No direct comparison between groups<br>P = 0.009 for change from baseline with flutamide plus metformin | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and flutamide (250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with | **Mean reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>14.5 to 7.9 with flutamide plus metformin<br>9.3 to 8.0 with placebo<br>39 women in this analysis | P <0.001 for flutamide plus metformin *v* placebo | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | | | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and flutamide (250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Mean reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>14.5 to 7.9 with flutamide plus metformin<br>9.3 to 8.0 with placebo<br>39 women in this analysis | P <0.001 for flutamide plus metformin *v* placebo | | |

## Menstrual frequency

*Flutamide plus metformin compared with placebo* Flutamide plus metformin may be more effective than placebo at improving menstrual frequency at 6 and 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Menstrual frequency** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and flutamide (250 mg twice daily)<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in menstrual frequency from baseline , 6 months**<br>with flutamide plus metformin<br>with placebo<br>Absolute results reported graphically | P = 0.04 | ○○○ | flutamide plus metformin |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and flutamide (250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in mean number of menses from baseline , 6 months**<br>2.8 to 4.3 with flutamide plus metformin<br>2.7 to 3.2 with placebo<br>39 women in this analysis | P = 0.04 | ○○○ | flutamide plus metformin |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated metformin (850 mg twice daily) and flutamide (250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in mean number of menses from baseline , 12 months**<br>2.8 to 5.8 with flutamide plus metformin<br>2.7 to 3.2 with placebo<br>39 women in this analysis | P <0.001 | ○○○ | flutamide plus metformin |

## Adverse effects

No data from the following reference on this outcome. [22] [23]

**Further information on studies**

[23] The RCT reported that women were excluded if they were on any medication, if they had a significant change in body weight, or if they were dieting in the previous 3 months. However, it is not clear whether the 40 women from the earlier study had a treatment washout period, whether they continued on the same treatment, or whether they would have received the same treatment after randomisation.

**Comment:** The combination of flutamide and metformin only maintained the specific effect of each drug, and the effects were not additional or synergistic. [23]

**Clinical guide:**
Flutamide is not used as first-line treatment because of the possibility of fatal hepatic effects and the need for monitoring treatment.

## OPTION WEIGHT LOSS

- For GRADE evaluation of interventions for PCOS, see table, p 43 .
- We don't know whether weight loss improves clinical outcomes in women with PCOS.

## Benefits and harms

### Interventions to achieve weight loss versus no intervention:

We found no systematic review or RCTs.

### Different diets versus each other:

We found one RCT comparing two diets to achieve weight loss: high-protein (40% carbohydrate, 30% protein) versus low-protein (55% carbohydrate, 15% protein) for 16 weeks. [25]

#### Hirsutism

*High-protein compared with low-protein diet* We don't know whether a high-protein diet aimed at achieving weight loss is more effective than a low-protein diet at reducing hirsutism (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [25]<br>RCT | [25] | **Mean Ferriman–Gallwey score**<br>with high-protein diet (40% carbohydrate, 30% protein)<br>with low-protein diet (55% carbohydrate, 15% protein)<br>Absolute results not reported<br>The RCT combined results from both diets and assessed changes in both groups from baseline | No direct comparison between groups<br>Mean increase from baseline from 19.5 to 19.7 with diet (results from both diets combined)<br>P value not reported | | |

#### Menstrual frequency

*High-protein compared with low-protein diet* We don't know whether a high-protein diet aimed at achieving weight loss is more effective than a low-protein diet at improving menstrual patterns (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Menstrual frequency** | | | | | |
| [25]<br>RCT | 28 women with PCOS | **Improvement in menstrual pattern**<br>with high-protein diet (40% carbohydrate, 30% protein)<br>with low-protein diet (55% carbohydrate, 15% protein)<br>Absolute results not reported<br>The RCT combined results from both diets and assessed changes in both groups from baseline | No direct comparison between groups<br>11/25 (44%) women had improvement menstrual frequency with diet (results of both diets combined)<br>P value not reported | | |

**Adverse effects**

No data from the following reference on this outcome. [25]

**Further information on studies**

**Comment:** Obesity and hyperinsulinaemia play a key role in the development of PCOS. Weight loss could, therefore, be of help in its management. We found one RCT that assessed adding metformin to a weight-loss diet. [26] Unfortunately, it did not assess clinical outcomes of weight loss; for clinical outcomes of adding metformin to weight loss, see option on metformin, p 29 . More RCTs assessing interventions to achieve weight loss in women with PCOS are needed.

## OPTION KETOCONAZOLE

- For GRADE evaluation of interventions for PCOS, see table, p 43 .
- We found no direct information from RCTs about the effects of ketoconazole in women with PCOS.
- We don't know whether ketoconazole is effective at reducing hirsutism compared with other treatments.

### Benefits and harms

**Ketoconazole versus placebo:**

We found no systematic review or RCTs.

**Ketoconazole versus cyproterone acetate–ethinylestradiol, cyproterone acetate–ethinylestradiol plus sequential cyproterone acetate, or spironolactone:**

See option on cyproterone acetate–ethinylestradiol, p 3 .

**Further information on studies**

**Comment:** None.

## OPTION MECHANICAL HAIR REMOVAL

- For GRADE evaluation of interventions for PCOS, see table, p 43 .
- Mechanical hair removal with certain types of lasers may be effective in the short term (6 months), but longer-term effects are less clear.

## Benefits and harms

### High-intensity laser treatment versus control:

We found one systematic review (search date 2005, 11 RCTs, 444 women, number of women with PCOS not stated) examining the effects of laser epilation and photoepilation for unwanted hair growth. [27] A meta-analysis could not be performed because of heterogeneity in interventions and outcomes assessed. The RCTs were not of good methodological quality and the methods of randomisation were unclear or inadequate.

#### Hirsutism

*High-intensity compared with low-intensity laser treatment* High-intensity laser treatment may be more effective at 6 months than low-intensity laser treatment at reducing facial hirsutism in women with PCOS (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [28] Systematic review **Crossover design** | 88 women with PCOS Data from 1 RCT | **Mean improvement in self-reported hirsutism from baseline measured on a scale of 1 (least severe) to 10 (most severe) , 6 months** 7.3 to 3.6 with high-intensity laser treatment 7.1 to 6.1 with low-intensity laser treatment High-intensity laser treatment (average of 4.8 treatments at 23.6 J/cm$^2$) versus control (low-intensity laser treatment; average of 4.4 treatments at 4.8 J/cm$^2$) | P <0.05 | ○○○ | high-intensity laser treatment |

#### Menstrual effects

No data from the following reference on this outcome. [28]

#### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [28] Systematic review | 88 women with PCOS Data from 1 RCT | **Adverse effects** with high-intensity laser treatment with low-intensity laser treatment The review reported that adverse effects were infrequent, and in- | Signficance not assessed | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | cluded pain, redness, swelling, pigmentary changes, and burned hairs | | | |

**Further information on studies**

**Comment:** Mechanical methods of hair removal searched for by *Clinical Evidence* included epilators, depilatory creams or lotions, waxing, electrolysis, and laser treatment. There was insufficient evidence for an effect with intense pulsed light, neodymium:YAG, or ruby lasers. Long-term effects on hair removal were not reported for any treatment.

## OPTION METFORMIN

- For GRADE evaluation of interventions for PCOS, see table, p 43 .
- Metformin in selected patients (who have abnormal luteinising hormone [LH]/follicle-stimulating hormone [FSH] ratios) may improve menstrual pattern and oligomenorrhoea.
- The results of RCTs comparing metformin with placebo are conflicting for menstrual frequency and hirsutism.
- Metformin, alone or combined with cyproterone acetate–ethinylestradiol (co-cyprindiol), may be more effective than cyproterone acetate–ethinylestradiol alone at reducing hirsutism.
- Metformin combined with flutamide reduces hirsutism scores and improves menstrual frequency compared with placebo, but we don't know how the individual drugs compare with each other.

## Benefits and harms

### Metformin versus placebo:

We found no systematic review, but found five RCTs. [22] [23] [29] [30] [26]

#### Hirsutism

*Metformin compared with placebo* We don't know whether metformin is more effective than placebo at reducing hirsutism at 6 to12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>with metformin (850 mg twice daily)<br>with placebo<br>Absolute results not reported<br>Number of women in this analysis unclear | No direct comparison between groups<br>P = 0.022 for change from baseline with metformin<br>P = 0.125 for change from baseline with placebo | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin plus flutamide (metformin 850 mg twice daily plus flutamide 250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Mean reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>13.0 to 10.9 with metformin<br>9.3 to 8.0 with placebo | No direct comparison between groups<br>P <0.01 with metformin from baseline<br>P <0.05 with placebo from baseline | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin plus flutamide (metformin 850 mg twice daily plus flutamide 250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Mean reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>13.0 to 10.4 with metformin<br>9.3 to 8.0 with placebo | No direct comparison between groups<br>P <0.01 with metformin from baseline<br>P <0.05 with placebo from baseline | | |
| [26]<br>RCT | 40 women, 20 with PCOS, all with BMI >28 | **Reduction in Ferriman–Gallwey score from baseline , 6 months** | No direct comparison between groups | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before metformin treatment | 14.8 to 12.9 with metformin (850 mg twice daily)<br>11.5 to 10.5 with placebo | P <0.05 with metformin from baseline<br>P value reported as not significant<br>CI not reported for placebo from baseline | | |

### Menstrual frequency

*Metformin compared with placebo* Metformin may be more effective than placebo at improving menstrual patterns at 3 to 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Menstrual frequency** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Improvement in menstrual frequency , 6 months**<br>with metformin (850 mg twice daily)<br>with placebo<br>Absolute results reported graphically<br>Number of women in this analysis unclear | P = 0.054 for metformin *v* placebo<br>Menstrual frequency significantly improved from baseline in women taking metformin | ⟷ | Not significant |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in mean number of menses , 6 months**<br>2.6 to 4.3 with metformin<br>2.7 to 3.2 with placebo<br>39 women in this analysis | P = 0.031 for metformin *v* placebo | ○○○ | metformin |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in mean number of menses , 12 months**<br>2.6 to 4.6 with metformin<br>2.7 to 3.2 with placebo<br>39 women in this analysis | P = 0.003 for metformin *v* placebo | ○○○ | metformin |
| [26]<br>RCT | 40 women, 20 with PCOS, all with BMI >28<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before metformin treatment | **Change from baseline in menstrual frequency , 6 months**<br>3.5 with metformin<br>2.2 with placebo | P <0.05 | ○○○ | metformin |
| [29]<br>RCT | 23 women with PCOS<br>See further information on studies for population details that may affect interpretation of results | **Substantial improvement in menstrual pattern , 3 months**<br>5/11 (45%) with metformin (500 mg twice daily)<br>0/12 (0%) with placebo<br>The RCT did not define substantial improvement in menstrual pattern | OR 12.88<br>95% CI 1.85 to 89.61 | ●●● | metformin |
| [30]<br>RCT | 143 anovulatory women with PCOS, BMI >30<br>All women were given a diet high in carbohydrates and low in fats with an aim to reduce caloric intake by 500 kcal/day | **Increase in frequency of menstruation , 6 months**<br>36/69 (52%) with metformin<br>43/74 (58%) with placebo | P = 0.60 | ⟷ | Not significant |

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [29]<br>Systematic review | 23 women with PCOS | **Adverse effects**<br>5 with metformin<br>2 with placebo<br>Adverse effects included nausea, diarrhoea, and heartburn | | | |
| [30]<br>RCT | 143 anovulatory women with PCOS, BMI >30 | **Adverse effects**<br>with metformin<br>with placebo<br>17 women withdrew from the study because of adverse effects (number of women from each group not reported and adverse effects not specified) | | | |

### Metformin versus cyproterone acetate–ethinylestradiol:

See option on cyproterone acetate–ethinylestradiol, p 3 .

### Metformin versus flutamide:

See option on flutamide, p 12 .

### Metformin plus cyproterone acetate–ethinylestradiol versus cyproterone acetate–ethinylestradiol alone:

See option on cyproterone acetate–ethinylestradiol, p 3 .

### Metformin plus flutamide versus placebo:

We found two RCTs comparing flutamide (250 mg twice daily), metformin (850 mg twice daily), metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily), and placebo. [22] [23]

#### Hirsutism

*Metformin plus flutamide compared with placebo* Metformin plus flutamide may be more effective than placebo at reducing hirsutism scores at 6 to 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin (850 mg twice daily)<br>All women were given a low-calorie (1200–1400 kcal/day) | **Reduction in Ferriman–Gallwey scores , 6 months**<br>with metformin plus flutamide (metformin 850 mg twice daily plus flutamide 250 mg twice daily)<br>with placebo<br>Absolute results reported graphically<br>Number of women in this analysis unclear | P = 0.009 | ○○○ | metformin plus flutamide |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | diet starting 1 month before treatment | | | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin (850 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Mean reduction in Ferriman–Gallwey scores , 6 months**<br>14.5 to 7.9 with metformin plus flutamide<br>9.3 to 8.0 with placebo<br>39 women in this analysis | P <0.001 | ○○○ | metformin plus flutamide |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin (850 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Mean reduction in Ferriman–Gallwey scores , 12 months**<br>14.5 to 6.5 with metformin plus flutamide<br>9.3 to 8.0 with placebo<br>39 women in this analysis | P <0.001 | ○○○ | metformin plus flutamide |

**Menstrual frequency**

*Metformin plus flutamide compared with placebo* Metformin plus flutamide may be more effective than placebo at improving menstrual frequency at 6 to 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Menstrual frequency** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin (850 mg twice daily)<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Improvement in menstrual frequency , 6 months**<br>with metformin plus flutamide (metformin 850 mg twice daily plus flutamide 250 mg twice daily)<br>with placebo<br>Absolute results reported graphically | P = 0.038 | ○○○ | metformin |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin (850 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in mean number of menses , 6 months**<br>2.8 to 4.3 with metformin plus flutamide<br>2.7 to 3.2 with placebo<br>39 women in this analysis | P = 0.044 | ○○○ | metformin plus flutamide |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin (850 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 | **Increase in mean number of menses , 12 months**<br>2.8 to 5.8 with metformin plus flutamide<br>2.7 to 3.2 with placebo<br>39 women in this analysis | P <0.001 | ●●○ | metformin plus flutamide |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | women who were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | | | | |

### Adverse effects

No data from the following reference on this outcome. [22] [23]

### Metformin plus flutamide versus metformin alone:

We found two RCTs comparing four interventions: metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily), metformin alone (850 mg twice daily), flutamide alone (250 mg twice daily), and placebo. [22] [23]

### Hirsutism

*Metformin plus flutamide compared with metformin alone* We don't know whether metformin plus flutamide is more effective than metformin alone at reducing hirsutism scores at 6 to 12 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and placebo<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>with metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>with metformin alone (850 mg twice daily)<br>Absolute results reported graphically<br>Number of women in this analysis unclear | No direct comparison between groups<br>P <0.001 with metformin plus flutamide from baseline<br>P = 0.022 with metformin alone from baseline | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and placebo<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either | **Mean reduction in Ferriman–Gallwey scores from baseline , 6 months**<br>14.5 to 7.9 with metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>13.0 to 10.9 with metformin alone (850 mg twice daily)<br>40 women in this analysis | No direct comparison between groups<br>P <0.001 with metformin plus flutamide from baseline<br>P <0.01 with metformin alone from baseline | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | drug alone or in combination with dieting, and 40 women who were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | | | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and placebo<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited<br>All women were given a low-calorie (1200–1400kcal/day) diet starting 1 month before treatment | **Mean reduction in Ferriman–Gallwey scores from baseline , 12 months**<br>14.5 to 6.5 with metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>13.0 to 10.4 with metformin alone (850 mg twice daily)<br>40 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with metformin plus flutamide<br>P <0.01 for change from baseline with metformin alone | | |

## Menstrual frequency

*Metformin plus flutamide compared with metformin alone* We don't know how metformin plus flutamide and metformin alone compare at improving menstrual frequency at 6 to 12 months (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Menstrual frequency** | | | | | |
| [22]<br>RCT<br>**4-armed trial** | 40 women, 20 with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin (850 mg twice daily)<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in menstrual frequency from baseline , 6 months**<br>with metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>with metformin alone (850 mg twice daily)<br>Absolute results reported graphically<br>Number of women in this analysis unclear | No direct comparison between groups<br>P value reported as significant with metformin plus flutamide from baseline<br>P <0.001 for metformin alone from baseline | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin (850 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment | **Increase in mean number of menses from baseline , 6 months**<br>2.8 to 4.3 with metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>2.6 to 4.3 with metformin alone (250 mg twice daily)<br>40 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with metformin plus flutamide<br>P <0.001 for change from baseline with metformin | | |
| [23]<br>RCT<br>**4-armed trial** | 80 overweight or obese women with PCOS, all with BMI >28<br>The remaining arms evaluated flutamide (250 mg twice daily) and metformin (850 mg twice daily)<br>The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [22] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited<br>All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment. | **Increase in mean number of menses from baseline , 12 months**<br>2.8 to 5.8 with metformin plus flutamide (metformin: 850 mg twice daily; flutamide: 250 mg twice daily)<br>2.6 to 4.6 with metformin alone (250 mg twice daily)<br>40 women in this analysis | No direct comparison between groups<br>P <0.001 for change from baseline with metformin plus flutamide<br>P <0.001 for change from baseline with metformin | | |

## Adverse effects

No data from the following reference on this outcome. [22] [23]

**Further information on studies**

[23] The RCT reported that women were excluded if they were on any medication, if they had a significant change in body weight, or if they were dieting in the previous 3 months. However, it is not clear whether the 40 women from the earlier study had a treatment washout period, whether they continued on the same treatment, or whether they would have received the same treatment after randomisation. The combination of flutamide and metformin only maintained the specific effect of each drug, and the effects were not additional or synergistic.

[29] Women taking placebo had a significantly higher BMI at baseline compared with women taking metformin (P <0.05). Women taking placebo also had higher fasting insulin than women taking metformin (P value reported as not significant) but similar insulin sensitivity. This may have biased results in favour of metformin.

**Comment:** **Clinical guide:**
Although metformin plus flutamide is effective in reducing hirsutism, this would not be considered a primary indication for treatment.

## OPTION SPIRONOLACTONE

- For GRADE evaluation of interventions for PCOS, see table, p 43 .
- Spironolactone may reduce hirsutism compared with placebo, and seems as effective as finasteride or cyproterone acetate–ethinylestradiol.

## Benefits and harms

### Spironolactone versus placebo:

We found one systematic review (search date 2003, 2 RCTs, 78 women, 21 with PCOS) comparing spironolactone versus placebo for 6 months. [31]

#### Hirsutism

*Spironolactone compared with placebo* Spironolactone may be more effective than placebo at reducing hirsutism at 6 months in women with idiopathic hirsutism or hirsutism attributed to PCOS (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [31] Systematic review | 78 women, 21 with PCOS<br>2 RCTs in this analysis | **Proportion of women reporting subjective improvement , 6 months**<br>12/21 (57%) with spironolactone (100 mg)<br>3/21 (14%) with placebo | OR 7.18<br>95% CI 1.96 to 26.28 | ●●● | spironolactone |
| [31] Systematic review | 78 women, 21 with PCOS<br>2 RCTs in this analysis | **Improvement in Ferriman–Gallwey score , 6 months**<br>with spironolactone (100 mg)<br>with placebo<br>Absolute results not reported | WMD –7.20<br>95% CI –10.98 to –3.42 | ○○○ | spironolactone |

#### Menstrual frequency

No data from the following reference on this outcome. [31]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [31]<br>Systematic review | 78 women, 21 with PCOS<br>Data from 1 RCT | **Adverse effects**<br>with with spironolactone (100 mg)<br>with placebo<br>Adverse effects of spironolactone may include polyuria, fatigue, nausea, headache, decreased libido, and sexual dysfunction<br>In 1 RCT identified by the review, 3 women taking spironolactone withdrew from the trial because of menorrhagia | | | |

**Spironolactone versus cyproterone acetate–ethinylestridiol, cyproterone acetate–ethinylestridiol plus sequential cyproterone acetate, or ketocanazole:**

See option on cyproterone acetate–ethinylestradiol, p 3 .

**Spironolactone versus finasteride:**

We found one systematic review (as above, search date 2003, 2 RCTs). [31] The review identified one RCT. [16]

### Hirsutism

*Spironolactone compared with finasteride* We don't know how spironolactone and finasteride compare at reducing hirsutism in women with PCOS (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Hirsutism** | | | | | |
| [16]<br>RCT<br>**4-armed trial** | 40 women, 21 with PCOS | **Hirsutism**<br>with spironolactone (100 mg daily)<br>with finasteride (250 mg daily)<br>with finasteride (5 mg daily)<br>with placebo<br>Absolute results reported graphically | Reported as not significant<br>P value not reported<br>All active treatments reduced hirsutism from baseline<br>The RCT may have been underpowered to detect a clinically important difference among treatments | ⟷ | Not significant |

### Menstrual frequency

No data from the following reference on this outcome. [16]

### Adverse effects

No data from the following reference on this outcome. [16]

**Spironolactone versus flutamide:**
See option on flutamide, p 12 .

**Spironolactone plus flutamide versus spironolactone alone:**
See option on finasteride, p 8 .

**Further information on studies**

**Comment:** The included trials were small, and confidence intervals were wide, so firm conclusions of treatment effectiveness could not be drawn. Although the RCTs included women with idiopathic hirsutism (hirsutism in women with regular, ovulatory menstrual cycles, and normal circulating androgen levels), it is likely that the results are generalisable to women with hirsutism attributed to PCOS.

## GLOSSARY

**Oligomenorrhoea** is infrequent or scanty menstruation.

**Hirsutism** The presence of excessive male-pattern hair growth in women on the face, chest, linea alba, or lower back. It usually occurs in women with polycystic ovary syndrome (PCOS), but "idiopathic hirsutism" may occur in women with regular menstrual cycles and normal circulating androgen levels.

**Low-quality evidence** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low-quality evidence** Any estimate of effect is very uncertain.

## SUBSTANTIVE CHANGES

**Cyproterone acetate–ethinylestradiol:** One systematic review [12] added. The systematic review found no significant difference in hirsutism scores between metformin and cyproterone acetate–ethinylestradiol. The review found that cyproterone acetate combined with metformin was more effective over 4 months at reducing hirsutism scores compared with cyproterone acetate–ethinylestradiol alone. Categorisation unchanged (Trade-off between benefits and harms).

**Flutamide:** Two RCTs added. [23] [24] The RCTs found that flutamide alone and flutamide plus metformin were more effective at reducing hirsutism scores and at improving menstrual frequency. Categorisation unchanged (Likely to be beneficial).

**Mechanical hair removal:** One systematic review added. [27] The systematic review found that, in the short term, alexandrite and diode lasers reduced hair reduction by about 50% up to 6 months after treatment. The evidence for the effects on hair removal of intense pulsed light, neodymium:YAG, or ruby lasers was insufficient. Categorisation unchanged (Unknown effectiveness).

**Metformin:** One systematic review [12] and two RCTs added. [23] [30] The systematic review found that cyproterone acetate plus metformin reduced hirsutism scores compared with cyproterone acetate–ethinylestradiol alone over 4 months. The RCTs reported conflicting evidence about the effects of metformin alone compared with placebo at improving menstrual frequency, but found that metformin plus flutamide improved menstrual frequency and reduced hirsutism scores compared with placebo. Categorisation unchanged (Likely to be beneficial).

## REFERENCES

1. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* 1997;18:774–800.[PubMed]
2. Legro RS, Driscoll D, Strauss JF 3rd, et al. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. *Proc Natl Acad Sci U S A* 1998;95:14956–14960.[PubMed]
3. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19:41–47.[PubMed]
4. Alvarez-Blasco F, Botella-Carretero JI, San Millan JL, et al. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. *Arch Intern Med* 2006;166:2081–2086.[PubMed]
5. Kahsar-Miller MD, Nixon C, Boots LR, et al. Prevalence of polycystic ovary syndrome (PCOS) in first-degree relatives of patients with PCOS. *Fertil Steril* 2001;75:53–58.[PubMed]
6. Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med* 2001;111:607–613.[PubMed]

7. Pierpoint T, McKeigue PM, Isaacs AJ, et al. Mortality of women with polycystic ovary syndrome at long-term follow-up. *J Clin Epidemiol* 1998;51:581–586.[PubMed]
8. Hardiman P, Pillay OS, Atiomo W. Polycystic ovary syndrome and endometrial carcinoma. *Lancet* 2003;361:1810–1812.[PubMed]
9. Niwa K, Imai A, Hashimoto M, et al. A case-control study of uterine endometrial cancer of pre- and post-menopausal women. *Oncol Rep* 2000;7:89–93.[PubMed]
10. Van der Spuy ZM, le Roux PA. Cyproterone acetate for hirsutism. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002; primary source the Cochrane Menstrual Disorders and Subfertility Group trials register.[PubMed]
11. Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. *Fertil Steril* 2002;77:919–927.[PubMed]
12. Costello M, Shrestha B, Eden J, et al. Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. In: The Cochrane Library, issue 4, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2005.[PubMed]
13. Tartagni M, Schonauer LM, De Salvia MA, et al. Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. *Fertil Steril* 2000;73:718–723.[PubMed]
14. World Health Organization. WHO Pharmaceuticals Newsletter. 2003;3:5. Available at http://www.who.int/medicines/publications/newsletter/en/news2003_3.pdf (last accessed 12 August 2008).
15. Lakryc EM, Motta ELA, Soares JM Jr, et al. The benefits of finasteride for hirsute women with polycystic ovary syndrome or idiopathic hirsutism. *Gynecol Endocrinol* 2003;17:57–63.[PubMed]
16. Moghetti P, Tosi F, Tosti A, et al. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000;85:89–94.[PubMed]
17. Falsetti L, De Fusco D, Eleftheriou G, et al. Treatment of hirsutism by finasteride and flutamide in women with polycystic ovary syndrome. *Gynecol Endocrinol* 1997;11:251–257.[PubMed]
18. Falsetti L, Gambera A, Legrenzi L, et al. Comparison of finasteride versus flutamide in the treatment of hirsutism. *Eur J Endocrinol* 1999;141:361–367.[PubMed]
19. Muderris II, Bayram F, Guven M. A prospective, randomized trial comparing flutamide (250 mg/d) and finasteride (5 mg/d) in the treatment of hirsutism. *Fertil Steril* 2000;73:984–987.[PubMed]
20. Beigi A, Sobhi A, Zarrinkoub F. Finasteride versus cyproterone acetate-estrogen regimens in the treatment of hirsutism. *Int J Gynaecol Obstet* 2004;87:29–33.[PubMed]
21. Kelestimur F, Everest H, Unluhizarci K, et al. A comparison between spironolactone and spironolactone plus finasteride in the treatment of hirsutism. *Eur J Endocrinol* 2004;150:351–354. [PubMed]
22. Gambineri A, Pelusi C, Genghini S, et al. Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol* 2004;60:241–249.[PubMed]
23. Gambineri A, Patton L, Vaccina A, et al. Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. *J Clin Endocrinol Metab* 2006;91:3970–3980.[PubMed]
24. Calaf J, Lopez E, Millet A, et al. Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: a 12-month, double-blind, parallel clinical trial. *J Clin Endocrinol Metab* 2007;92:3446–3452.[PubMed]
25. Moran LJ, Noakes M, Clifton PM, et al. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88:812–819.[PubMed]
26. Pasquali R, Gambineri A, Biscotti D, et al. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000;85:2767–2774.[PubMed]
27. Haedersdal M, Gotzsche PC. Laser and photoepilation for unwanted hair growth. In: The Cochrane Library, Issue 4, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.[PubMed]
28. Clayton WJ, Lipton M, Elford J, et al. A randomized controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. *Br J Dermatol* 2005;152:986–992.[PubMed]
29. Moghetti P, Castello R, Negri C, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 2000;85:139–146[PubMed]
30. Tang T, Glanville J, Hayden CJ, et al. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. *Human Reprod* 2006;21:80–89.[PubMed]
31. Farquhar C, Lee O, Toomath R, et al. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2003. Primary sources Medline, Bioabstracts, Psychlit, Cinahl, Social Sciences Index, Dissertation Abstracts, Current Contents, Embase, hand searches of reference lists of relevant trials, and personal contact with drug companies.[PubMed]

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## Disclaimer

**GRADE** **Evaluation of interventions for PCOS.**

| Important outcomes | | | Hirsutism, Menstrual effects, Menstrual frequency | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Studies (Participants) | Outcome | Comparison | Type of evidence | Quality | Consistency | Directness | Effect size | GRADE | Comment |
| *What are the effects of treatments in women with PCOS?* | | | | | | | | | |
| 1 (20) [10] | Hirsutism | Cyproterone acetate–ethinylestradiol versus placebo | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and subjective assessment of improvement |
| 1 (28) [11] | Hirsutism | Cyproterone acetate–ethinylestradiol versus combined oral contraceptives | 4 | –3 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data, incomplete reporting of results, and inclusion of women aged <18 years. Directness point deducted for no direct comparison between groups |
| 2 (35) [12] | Hirsutism | Cyproterone acetate–ethinylestradiol versus metformin | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and inclusion of open-label RCTs. Directness point deducted for inclusion of women without clinically diagnosed hirsutism |
| 1 (50) [13] | Hirsutism | Cyproterone acetate–ethinylestradiol plus finasteride versus cyproterone acetate–ethinylestradiol alone | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of women without PCOS |
| 1 (40) [13] | Hirsutism | Cyproterone acetate–ethinylestradiol plus metformin versus cyproterone acetate–ethinylestradiol alone | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for sparse data. Directness point deducted for inclusion of women without clinically diagnosed PCOS |
| 2 (64) [15] [16] | Hirsutism | Finasteride versus placebo | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of women without PCOS |
| 4 (264) [16] [17] [18] [19] | Hirsutism | Finasteride versus flutamide | 4 | –1 | –1 | –2 | 0 | Very low | Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness points deducted for inclusion of women without PCOS and for no direct comparison between groups |
| 1 (40) [20] | Hirsutism | Finasteride versus cyproterone acetate–ethinylestradiol | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for sparse data. Directness point deducted for inclusion of women without PCOS |
| 1 (65) [21] | Hirsutism | Finasteride plus spironolactone versus spironolactone alone | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of women with hirsutism other than due to PCOS |
| 4 (235) [16] [22] [23] [24] | Hirsutism | Flutamide versus placebo | 4 | –2 | 0 | –2 | 0 | Very low | Quality points deducted for incomplete reporting of results and for methodological weaknesses. Directness points deducted for inclusion of women without PCOS and for inclusion of other interventions |
| 2 (76) [22] [23] | Menstrual frequency | Flutamide versus placebo | 4 | –3 | 0 | –2 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results and for methodological weaknesses. Directness points deducted for inclusion of women without PCOS and for inclusion of other interventions |

| Important outcomes | | | Hirsutism, Menstrual effects, Menstrual frequency | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Studies (Participants) | Outcome | Comparison | Type of evidence | Quality | Consistency | Directness | Effect size | GRADE | Comment |
| 2 (77) [22] [23] | Hirsutism | Flutamide versus metformin | 4 | –2 | 0 | –2 | 0 | Very low | Quality points deducted for sparse data and for methodological weaknesses. Directness points deducted for no direct comparison between groups and for inclusion of other interventions |
| 2 (77) [22] [23] | Menstrual frequency | Flutamide versus metformin | 4 | –1 | 0 | –2 | 0 | Very low | Quality point deducted for sparse data. Directness points deducted for inclusion of other interventions and for no direct comparison between groups |
| 1 (40) [16] | Hirsutism | Flutamide versus spironolactone | 4 | –2 | 0 | –2 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness points deducted for inclusion of women without PCOS and for no direct comparison between groups |
| 2 (77) [22] [23] | Hirsutism | Flutamide versus flutamide plus metformin | 4 | –2 | 0 | –2 | 0 | Very low | Quality points deducted for sparse data and for methodological weaknesses. Directness points deducted for no direct comparison between groups and for inclusion of other interventions |
| 2 (77) [22] [23] | Menstrual frequency | Flutamide versus flutamide plus metformin | 4 | –2 | 0 | –2 | 0 | Very low | Quality points deducted for sparse data and for methodological weaknesses. Directness point deducted for no direct comparison between groups and for inclusion of other interventions |
| 2 (79) [22] [23] | Hirsutism | Flutamide plus metformin versus placebo | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and for methodological weaknesses. Directness point deducted for inclusion of other interventions |
| 2 (120) [23] | Menstrual frequency | Flutamide plus metformin versus placebo | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and for methodological weaknesses. Directness point deducted for inclusion of other interventions |
| 1 (28) [25] | Hirsutism | Different diets versus each other | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between groups |
| 1 (25) [25] | Menstrual frequency | Different diets versus each other | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between groups |
| 1 (88) [28] | Hirsutism | High-intensity laser treatment versus control | 4 | –3 | 0 | 0 | 0 | Very low | Quality points deducted for sparse data, weak methodology, and subjective assessment |
| 3 (119) [22] [23] [26] | Hirsutism | Metformin versus placebo | 4 | –3 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data, incomplete reporting of results, and methodological weaknesses. Directness point deducted for inclusion of other interventions |
| 5 (285) [22] [26] [29] [30] [23] | Menstrual frequency | Metformin versus placebo | 4 | –2 | –1 | –2 | 0 | Very low | Quality points deducted for incomplete reporting of results and methodological weaknesses. Consistency point deducted for conflicting results. Directness points deducted for inclusion of other interventions and for no direct comparison between groups |
| 2 (79) [22] [23] | Hirsutism | Metformin plus flutamide versus placebo | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and methodological weaknesses. Directness point deducted for inclusion of other interventions |
| 2 (79) [22] [23] | Menstrual frequency | Metformin plus flutamide versus placebo | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and methodological weaknesses. Directness point deducted for inclusion of other interventions |
| 2 (77) [22] [23] | Hirsutism | Metformin plus flutamide versus metformin alone | 4 | –2 | 0 | –2 | 0 | Very low | Quality points deducted for sparse data and methodological weaknesses. Directness points deducted for no direct comparison between groups and for inclusion of other interventions |

| Important outcomes | | | Hirsutism, Menstrual effects, Menstrual frequency | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Studies (Participants) | Outcome | Comparison | Type of evidence | Quality | Consistency | Directness | Effect size | GRADE | Comment |
| 2 (77) [22] [23] | Menstrual frequency | Metformin plus flutamide versus metformin alone | 4 | –2 | 0 | –2 | 0 | Very low | Quality points deducted for sparse data and methodological weaknesses. Directness points deducted for no direct comparison between groups and for inclusion of other interventions |
| 2 (78) [31] | Hirsutism | Spironolactone versus placebo | 4 | –1 | 0 | –1 | 0 | Low | Quality point deducted for sparse data. Directness point deducted for inclusion of women without PCOS |
| 1 (40) [16] | Hirsutism | Spironolactone versus finasteride | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and incomplete reporting of results |

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.